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OPTICAL METHOD FOR MONITORING ARTERIAL BLOOD HEMATOCRIT

Abstract:

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An apparatus and method of measuring blood hematocrit which involves directing first and second wavelengths of light through a blood sample, determining the ratio between pulsatile and non-pulsatile diffuse transmittances measured at each of the first and second wavelengths of light from the blood sample, and determining blood hematocrit of the blood sample from the ratio between pulsatile and non-pulsatile diffuse transmittances measured at each of the first and second wavelengths of light from the blood sample. One of the first and second wavelengths of light is within the isobestic region of oxyhemoglobin and the other is within the isobestic region of deoxyhemoglobin. A tissue phantom for simulating optical properties of a perfused finger is used to test the method and apparatus.

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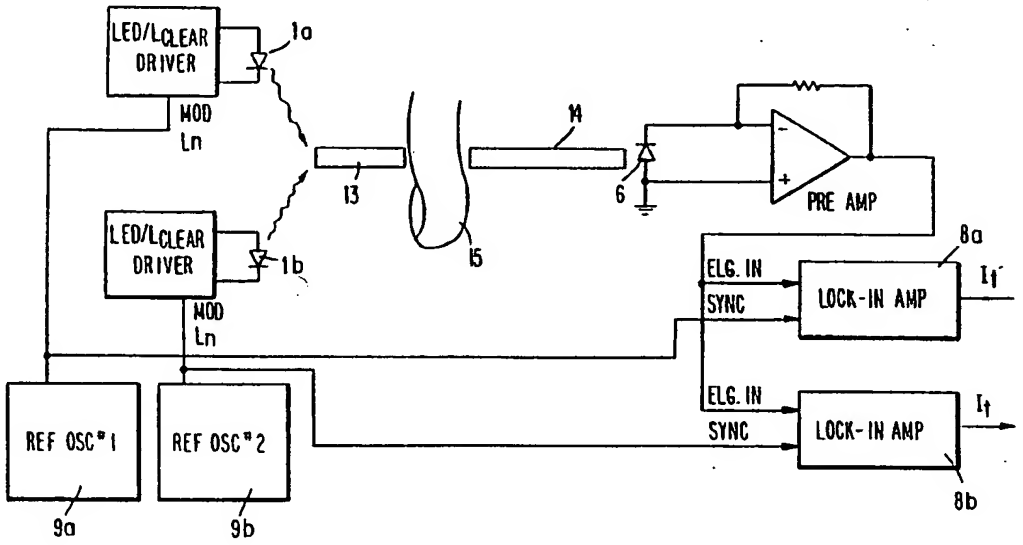

(57) Abstract

An apparatus and method of measuring blood hematocrit which involves directing first and second wavelengths of light through a blood sample, determining the ratio between pulsatile and non-pulsatile diffuse transmittances measured at each of the first and second wavelengths of light from the blood sample, and determining blood hematocrit of the blood sample from the ratio between pulsatile and non-pulsatile diffuse transmittances measured at each of the first and second wavelengths of light from the blood sample. One of the first and second wavelengths of light is within the isobestic region of oxyhemoglobin and the other is within the isobestic region of deoxyhemoglobin. A tissue phantom for simulating optical properties of a perfused finger is used to test the method and apparatus.

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OPTICAL METHOD FOR MONITORING ARTERIAL BLOOD HEMATOCRIT

Technical Field

The present invention relates to methods and apparatus for measuring blood hematocrit. More particularly, the present invention relates to non-invasive methods and apparatus for measuring hemoglobin concentration.

Background Art

Anemia is associated with many pathological conditions that result in a loss or reduced production of red blood cells, including renal failure, bone-marrow aplasia secondary to radiation therapy, and red-cell sickling. Although rarer, excessive production of red cells (polycythemia) is also seen clinically in patients with congenital heart disease and pulmonary emphysema. Arterial blood hematocrit or hemoglobin concentration values obtained from blood samples are used by clinicians to assist in the diagnosis of these abnormalities.

Several methods presently exist for measuring blood hematocrit or hemoglobin concentration, but all require either blood sampling or catheterization. The following methods are those most often used in clinical

laboratories to measure blood hematocrit or hemoglobin concentration: determination of packed-cell volume (PCV) by centrifugation of blood-filled capillary tubes; measurement of the volume fraction of red cells by automated cell counting techniques; and spectrophotometric assay of total hemoglobin content in lysed blood samples.

Although not widely applied, other simpler and more rapid techniques have been developed which are based on the measurement of diffuse light transmitted through undiluted whole blood samples (Schmitt et al, "New Methods for Whole Blood Oximetry", Ann. Biomed. Engin., Vol. 14 (1986), pages 35-52; Steinke et al, "Reflectance Measurements of Hematocrit and Oxyhemoglobin Saturation", Am. J. Physiol., Vol. 253 (1987), pages H147-153).

Repeated blood sampling is not acceptable for continuous monitoring or field screening applications. Moreover, repeated blood sampling is associated with an increased risk of HIV or hepatitis infection. Even the loss of the small quantities of blood which are required to make hematocrit measurements can be harmful to neonates. As alternatives, catheter-based sensors for whole-blood hematocrit monitoring have been developed (U.S. Patent No. 4,776,340 to Moran et al). However, because they require contact with circulating blood, catheter-based sensors may lead to more serious complications. Possible detrimental effects of long-term monitoring using arterial catheters include damage to blood vessels and production of thrombi or emboli.

In pulse oximetry (Yoshiya et al, "Spectrophotometric Monitoring of Arterial Oxygen Saturation in the Fingertip", Med. Biol. Eng. Comput.,

Vol. 18 (1980), pages 27-32; Tremper et al, "Pulse Oximetry", Anesthesiology, Vol. 70 (1989), pages 98-108), blood-perfused skin is illuminated with red and near-infrared light, and the ratio between the pulsatile (ac) and non-pulsatile (dc) diffuse transmittances measured at each wavelength is recorded. Hemoglobin oxygen saturation is determined from the measured red/infrared ac-dc ratio using an empirical mathematical relationship.

During the course of the present invention, the feasibility of non-invasive methods for determining arterial blood hematocrit was studied using theoretical and experimental models. The method according to the present invention provides a means of applying pulse oximetry principles to measure blood hematocrit.

Disclosure of the Invention

It is accordingly one object of the present invention to provide a method of measuring blood hematocrit.

Another object of the present invention is to provide a non-invasive method of measuring blood hematocrit.

A further object of the present invention is to provide a method of simultaneously measuring oxygen saturation and hemoglobin concentration of blood.

An even further object of the present invention is to provide an apparatus for measuring blood hematocrit.

A still further object of the present invention is to provide an apparatus for non-invasively measuring blood hematocrit.

A still further object of the present invention is to provide a tissue phantom which simulates the optical properties of a perfused finger.

According to these and further objects which will become apparent as the description of the present invention is presented below, the present invention provides a method of measuring blood hematocrit which involves:

directing first and second wavelengths of light through a blood sample;

determining the ratio between pulsatile and non-pulsatile diffuse transmittances measured at each of the first and second wavelengths of light from the blood sample; and

determining blood hematocrit of the blood sample from the ratio between pulsatile and non-pulsatile diffuse transmittances measured at each of the first and second wavelengths of light from the blood sample.

The present invention further provides an apparatus for measuring blood hematocrit which includes:

a sample holder for receiving a blood sample;

a first light generating means for generating light within the isobestic region of oxyhemoglobin:

a second light generating means for generating light within the isobestic region of deoxyhemoglobin;

means for directing light from the first and second light generating means to the sample holder;

means for receiving light from the sample holder;

means for measuring pulsatile and non-pulsatile diffuse transmittances from the sample holder; and

means for determining ratios of the measured pulsatile and non-pulsatile diffuse transmittances from the sample holder.

In addition, the present invention also provides a tissue phantom for simulating optical properties of a perfused finger which includes two interwoven networks of randomly distributed tubes, wherein one of the tube networks is filled with a fixed volume of a blood standard and another of the tube networks is adapted to be injected with a blood standard to simulate a pulsatile increase in blood volume.

Brief Description of Drawings

The present invention with be described with reference to the attached drawings which are given by way of non-limiting examples only, in which:

Figure 1 is an absorption spectra of water, deoxygenated red blood cells (Hb), and oxygenated red blood cells (HbO_2) in the 700 nm to 1350 nm spectral region.

Figure 2 is a schematic diagram of an apparatus for measuring the hematocrit of blood according to one embodiment of the present invention.

Figure 3 is a schematic illustration of a tissue phantom which simulates the optical properties of a perfused finger according to one embodiment of the present invention.

Figure 4 is a schematic diagram of an apparatus for measuring the hematocrit of blood according to another embodiment of the present invention.

Figure 5a is a graph of optical transmissions of whole blood at 800 nm and 1300 nm at various hemoglobin concentrations.

Figure 5b is a graph of the ratio between the optical densities of Fig. 5a at various hemoglobin concentrations.

Figure 6 is a graph which compares theoretical predictions of measurements of blood hematocrit with experimental test results.

Best Mode for Carrying out the Invention

Blood hematocrit (Hct) is routinely determined in clinics by analysis of blood samples. The present invention provides a non-invasive method for measuring arterial blood hematocrit which, when combined with pulse oximetry, enables simultaneous monitoring of hemoglobin concentration and oxygen saturation. The present invention is based on the same principles underlying pulse oximetry, except according to the present invention, two light sources which emit close to isobestic wavelengths of oxy/deoxyhemoglobin in the near-infrared band are employed.

During the course of the present invention it has been discovered that hematocrit is related to the ratios of the pulsatile and non-pulsatile components of the diffuse intensity transmitted through a blood-perfused tissue at isobestic wavelengths of oxy/deoxyhemoglobin in the near-infrared band. Based upon the inventor's discovery, an apparatus as described below has been developed for non-invasively measuring hemoglobin concentration and oxygen saturation.

At wavelengths throughout most of the visible and near-infrared spectrum, the optical density of whole blood has a strong dependence on the density of red cells in the blood and on the concentration and

oxygenation state of the hemoglobin contained in the cells. As blood hematocrit changes, the optical density of whole blood is altered as a result of changes in both scattering and absorption.

The macroscopic absorption and transport-corrected scattering coefficients of whole blood, denoted here as μ_a^b and μ_s^{*b}, respectively, can be related to hematocrit as follows:

$$\mu_a^b = \frac{H}{v_i}\{S\sigma_a^{HbO_2} + (1-S)\,\sigma_a^{Hb}\} + (1-H)\,\mu_a^p \qquad (1)$$

$$\mu_s^{*b} = (\sigma_s^{rbc}/v_i)\, f(H) \qquad (2)$$

where

H = blood hematocrit (assumed to be equal to the volume fraction of red blood cells, neglecting the small fraction of white cells and other formed elements);

v_i = volume of a red blood cell (μm^3);

S = hemoglobin oxygen saturation;

$\sigma_a^{HbO_2}$ = absorption cross-section of an oxygenated red cell (μm^2);

σ_a^{Hb} = absorption cross-section of a deoxygenated red cell (μm^2);

σ_{st}^{rbc} = transport-corrected scattering cross-section of a red cell (μm^2);

μ_a^p = absorption coefficient of blood plasma (mm^{-1});

f(H) = function accounting for the effect of the volume fraction of red blood cells on the scattering coefficient. According to Steinke et al, "Diffusion

Model of the Optical Absorbance of Whole Blood", J. Opt. Soc. Am. A., Vol. 5 (1988), pages 813-822, f(H) = H(1-H)(1.4-H).

To simplify the above equations, the following assumptions can be made: a) in the range of wavelengths of interest (700 nm < λ < 1350 nm), the optical absorption of plasma equals that of water; b) the volume fraction of water inside of and outside of the red blood cell is approximately the same; and c) the absorption coefficient of blood equals that of an equal-proportioned solution of Hb, HbO_2, and water.

With these assumptions, Eqs. (1) and (2) can be simplified to obtain,

$$\mu_a^b = 5.0\ H\ \{S(\epsilon_o - \epsilon_r) + \epsilon_r\} + \mu_a^w \qquad (3)$$

$$\mu_s^{*b} = H\ (1-H)\ (1.4 - H)\ \mu_s'^{rbc} \qquad (4)$$

where μ_a^w is the absorption coefficient of water (mm^{-1}), and ϵ_o and ϵ_r are the millimolar extinction coefficients ($mM^{-1} \cdot L^{-1} \cdot cm^{-1}$) of oxyhemoglobin and deoxyhemoglobin, respectively, and μ_s^{*rbc} is the scattering coefficient of the red blood cell (mm^{-1}), defined as $\mu_s^{*rbc} = \sigma_{st}^{rbc}/v_i$. It is apparent from these equations that, if the underlying assumptions are valid, the absorption and scattering coefficients of whole blood depend only on hematocrit, oxygen saturation, and a constant factor representing absorptive losses due to water. Furthermore, at an isobestic wavelength (i.e., at a wavelength at which $\epsilon_o = \epsilon_r$), the absorption and scattering coefficients of blood do not depend on oxygen saturation. Therefore, at an isobestic wavelength, Eq. (3) becomes

$$\mu_a^b = 5.0\ H\epsilon^{Hb,iso} + \mu_a^w \qquad (5)$$

Figure 1 shows the absorption spectra of water, Hb, and HbO_2 in the 700 nm - 1350 nm spectral region, as measured by a Cary 17 dual-beam spectrophotometer. Water absorption in the Hb and HbO_2 solutions was subtracted. Note that there are two wavelength bands in the vicinity of 800 nm and 1300 nm within which $\epsilon_o = \epsilon_r$. The measurement of light absorption in blood at wavelengths in each of these two regions forms the basis of the present ratiometric scheme for determining the hematocrit of whole blood, independent of oxygen saturation. Although its existence was first reported by Barlow et al ("Absorption Measurements for Oxygenated and Reduced Haemoglobin in the Range 0.6 mm - 1.88 mm", Clin. Chem., Vol. 8 (1962), pages 67-71), the 1300 nm isobestic region has not been exploited heretofore. At λ = 800 nm, the absorption coefficient of water is negligible compared to that of hemoglobin; it follows from Eq. (5) that absorption in blood and hematocrit are proportionally related,

$$\mu_a^{b,800} = 5.0\ H\epsilon^{Hb,800} \qquad (6)$$

In the wavelength range $1300 < \lambda < 1350$ nm, water absorption greatly exceeds hemoglobin absorption. Because absorption by water in the blood is dominant at this wavelength, hemoglobin concentration has only a small effect on the total optical absorption of the blood. As a result, the absorption coefficient of blood is approximately equal to the absorption coefficient of water, thus,

$$\mu_a^{b,1300} = 5.0\ H\epsilon^{Hb,1300} + \mu^{w,1300}$$

$$= \mu^{w,1300} \qquad \text{for } \epsilon^{Hb,1300} \rightarrow 0 \qquad (7)$$

If whole blood did not scatter light, then the ratio of its optical density (OD) at 800 nm and 1300 nm would simply be linearly proportional to its hematocrit, regardless of the sample thickness (d), as follows

$$OD^{800}/OD^{1300} = \mu_a^{b,800}d/\mu_a^{b,1800}d = (5.0\ \epsilon^{Hb,800}/\mu_a^{w,1300})H \qquad (8)$$

However, because the red cells do indeed scatter light, the optical-density ratio has, in general, a more complicated dependence on d and H than that given by Eq. (8). Nonetheless, as shown below, the optical-density ratio has been observed to maintain its linear dependence on hematocrit provided that d is less than a few millimeters.

The technique of pulse oximetry has been shown to provide a satisfactory solution to the challenging problem of measuring changes in the optical absorption of blood contained in highly scattering skin tissues (Yoshiya, Vol. 18, supra; Tremper, Vol. 70, supra). To a first approximation, the pulsatile optical signals measured by a pulse oximeter result from changes in the bulk absorption coefficient of the skin induced by a transient increase in blood volume during cardiac systole. The blood-perfused tissue is treated as a homogeneous mixture of blood and bloodless skin tissues through which photons diffuse. Changes in the intensity measured by sources and detectors placed on the skin are calculated using a simple photon-diffusion theory. In

earlier studies, this approach has proven useful in the analysis of multiple scattering effects on pulse oximetry (Schmitt, "A simple Photon Diffusion Analysis of the Effects of Multiple Scattering on Pulse Oximetry", IEEE Trans. Biomed. Eng., Vol. 88 (1991), pages 1194-1203).

Consider a collimated beam (intensity I_o) of infinite extent incident on a slab of tissue, also of infinite extent. The photon density, $\Psi(x)$, in the slab (thickness d) can be described by the 1-D diffusion equation,

$$-D \frac{\Psi^2(x)}{dx^2} + \mu_a \Psi(x) = I_o \mu_s^* \exp[-(\mu_a+\mu_s^*)x] \qquad (9)$$

where μ_a and μ_s^*, respectively, are the absorption and transport-corrected scattering coefficients of the tissue and D is the diffusion coefficient, defined as $D = [3(\mu_a + \mu_s^*)]^{-1}$. The general solution to Eq. (9) is

$$\Psi(x) = I_o[k_1 \exp(-\mu_t x) + k_2 \exp(-\alpha x) + K_3 \exp(\alpha x)] \qquad (10)$$

Here, the reciprocal penetration depth, α, has been introduced which is given by $\alpha = \mu_a/D = 3\mu_s^*\mu_a)^{1/2}$ for $\mu_a << \mu_s^*$, and the total extinction coefficient, μ_t, is defined as $\mu_t = \mu_a + \mu_s^*$. For $\Psi(0) = \Psi(d) = 0$ (i.e., absorbing boundaries), the constants k_1, k_2 and k_3 are given by

$$k_1 = \mu_s^*/[D(\mu_t^2 - \alpha^2)] \quad (11a)$$

$$k_2 = -k_1\{[\exp(-\mu_t d)-\exp(\alpha d)]/[\exp(-\alpha d)-\exp(ad)]\} \quad (11b)$$

$$k_3 = k_1\{[1+\exp(-\mu_t d)-\exp(\alpha d)]/[\exp(-\alpha d)-\exp(\alpha d)]\} \quad (11c)$$

The diffuse intensity, I_t, received by a collimated detector located on the opposite side of the tissue slab can then be obtained as follows:

$$I_t = -D\frac{d}{dx}\Psi(x)\Big|_{x=d} = DI_o[k_1\mu_t\exp(-\mu_t x)+K_2\alpha\exp(-\alpha x)-k_3\alpha\exp(\alpha x)] \quad (12)$$

To simplify the analysis, the effect of changes in blood volume and hematocrit on the bulk scattering coefficient of the tissue are neglected and μ_s^* is treated as a constant having a range of values characteristic of a particular tissue type. In an idealized homogeneous tissue model, it is assumed that μ_a can be obtained by adding the absorption coefficients of the individual absorbers in the tissue, which mainly comprise hemoglobin, water, and assorted pigment chromophores. By limiting interest to intensities measured at isobestic wavelengths, it is unnecessary to distinguish the volume fractions of venous and arterial blood. With these assumptions, the total absorption coefficient is simply

$$\mu_a^t = V_b\mu_a^b + V_w\mu_a^w + (1-V_b - V_w)\mu_a^{bkg} \quad (13)$$

where V_b and V_w are the volume fractions of blood and water, and μ_a^{bkg} represents absorption by other

unspecified substances. Pulsatile flow into and out of the tissue produces a small increase in the absorption coefficient of the tissue proportional to the change in the blood volume fraction $\Delta\mu_a = \Delta V_b \mu_a^b$. As a result, a pulsatile ("ac") variation is superimposed on the time-averaged ("dc") intensity received by the detector. The ratio of the pulsatile to the average intensity is then,

$$I_{ac}/I_{dc}=\Delta I_t/I_t=[I_t\{\mu_a-\mu_a^t\}-I_t\{\mu_a-\mu_a^t+\Delta V_b\mu_a^b\}]/I_t\{\mu_a=\mu_a^t\} \quad (14)$$

If the transmitted intensity obeyed the Beer-Lambert law [i.e. $I_t = I_o \exp(-\mu_a d)$], this ratio would simply equal $\Delta V_b \mu_a^b$, and the ratio of the ac-dc ratios measured at two different wavelengths would directly yield the ratio of the absorption coefficients of the blood at the two wavelengths (Schmitt, Vol. 88, supra). However, as the above photon-diffusion analysis shows, I_t has a complicated dependence on the scattering properties of the tissue that is not accounted for by the Beer-Lambert law. Nevertheless, as pointed by other investigators (Cope et al, "Methods of Quantitating Cerebral Near-Infrared Spectroscopy Data", Adv. Exp. Med. Biol., Vol. 222 (1988), pages 183-190; Sevick et al, "Quantitation of Time- and Frequency-Resolved Optical Spectra for the Determination of Tissue Oxygenation", Anal. Biochem., Vol. 195 (1991), pages 330-351), if the mean path length can be determined for a specific set of conditions, a modified form of the Beer-Lambert law can still be applied. This can be seen from Eq. (12) by noting that $I_t \sim \exp[-3\mu_a\mu_s^*)^{1/2}d]$, for $d >> \alpha^{-1}$ and $\mu_a << \mu_s^*$. For a small change in tissue absorption, it follows that

$$I_{ac}/I_{dc} = -[(dI_t/d\mu_a)/I_t]\Delta\mu_a = \{(3\mu_s^*/4\mu_a)^{1/2}\}\Delta V_b \mu_s^b \quad (15)$$

The quantity enclosed in the brackets "{..}" in this equation is the same as the "differential path length factor", which was derived earlier by Cope et al (Vol. 222, supra), that relates attenuation in diffusive and non-scattering media. An estimate of the ratio of the absorption coefficients of blood at the two wavelengths can be obtained by measuring I_{ac} / I_{dc} at two wavelengths and forming the following ratio:

$$R = (I_{ac}/I_{dc})_{\lambda_1}/(I_{ac}/I_{dc})^{\lambda 2}$$

$$= \{(\mu_a^{\lambda 2}/\mu_a^{\lambda 1})^{1/2}(\mu_s^{*\lambda 1}/\mu_s^{*\lambda 2})^{1/2}\}\ (\mu_a^{b,\lambda 1}/\mu_a^{b,\lambda 2}) \quad (16)$$

For λ_1 = 800 nm and λ_2 = 1300 nm, R is a strong function of hematocrit because the dependence of $\mu_a^{b,800}$ on hemoglobin concentration greatly exceeds that of $\mu_a^{b,1300}$. Eq. (16) describes the effect of the wavelength-dependence of μ_s^* and μ_a on the relationship between R and the absorption ratio $\mu_a^{b,\lambda 1}/\mu_a^{b,\lambda 2}$. Accurate calibration of R as a function of this ratio requires that the bracketed quantity in this equation remain constant over the desired measurement range.

To theoretically determine the effects of the optical properties of skin on R measurements made at 800 nm and 1300 nm, its scattering and absorption coefficients at these wavelengths must be known. Several studies have shown that approximate values of μ_s^* and μ_s of skin tissue can be obtained from surface-reemittance measurements (Bonner et al, "Model for Photon Migration in Turbid Biological Media", J. Opt. Soc. Am. A., Vol. 4 (1987), pages 423-432; Schmitt et

al, "Multilayer Model of Photon Diffusion in Skin", J. Opt. Soc. Am. A., Vol. 7 (1980), pages 2141-2153). At a sufficiently large radial distance r from a point light source, the intensity I_r (r) re-emitted from the skin can be shown to decay as

$$I(r) = r^{-2} \exp \{-(3\mu_s^*\mu_a)^{1/2} r\} \quad (17)$$

The quantity $(3\ \mu_s^*\mu_a)^{1/2}$ at a particular wavelength can be obtained by fitting the slope of the In $[r^2 I(r)]$ - vs - r surface-reemittance curve. The ratio of the slopes measured at λ_2 and λ_1, yields the quantity $(\mu_a^{\lambda 2}/\mu_a^{\lambda 1})^{1/2}(\mu_s^{*\lambda 2}/\mu_s^{*\lambda 1})^{1/2}\}$, which is same as the bracketed quantity in Eq. (16), except the numerator and denominator of the ratio of the scattering coefficients is reversed. Therefore, an estimate of the ratio of the absorption coefficients at two wavelengths can be obtained, if μ_s^* is assumed to be the same at the two wavelengths or if the ratio of the scattering coefficients is known. Fortunately, according to the results of earlier theoretical and experimental studies, the transport-corrected scattering coefficient of most tissues is not a strong function of wavelength (Schmitt, Vol. 7, supra; Flock et al, "Total Attenuation Coefficients and Scattering Phase Functions of Tissues and Phantom Materials at 633 nm", Med. Phys., Vol. 14 (1987), pages 835-841).

Using an in vitro tissue model as discussed below, the feasibility of measuring the hematocrit of blood contained in a scattering medium using dual-wavelength photoplethysmography was examined. A limited number of in vivo measurements were also made to: a) estimate the optical coefficients of human skin that were needed to

design the in vitro model and b) record photoplethysmograms of individuals having normal hematocrit values to study the importance of physiological variations on calibration.

The experiments were carried out with the instrumentation diagrammed in Fig. 2. Light emitted by a pair of laser diodes 1a and 1b with peak emission wavelengths of 830 nm (Model LSX350-830-15, LaserMax Corp.) and 1300 nm (Model LSX350-1300-6, LaserMax Corp.) was collected by a bifurcated fiber bundle 2, expanded and collimated by lens 3 to project across aperture plate 4 so as to form a small, e.g., 1-cm, diameter beam for illumination of the light-scattering sample in cuvette 5. In some experiments, light-emitting diodes 1a and 1b with peak emission wavelengths of 800 nm (Marktech MTE1650) and 1300 nm (Epitaxx ETX1550T) were employed. A single photodiode 6 (e.g., an InGaAs photodiode) with an external collimating lenses 7 (aperture diameter = 2 mm) sampled scattered light transmitted through the tissue model sample. This optical configuration was chosen to approximate the plane-parallel conditions under which the photon-diffusion model discussed above was desired. Voltages proportional to scattered intensities at both wavelengths of each laser diode were measured simultaneously by a pair of lock-in amplifiers 8a, 8b, each referenced to the modulation frequency of one of the laser diodes by reference oscillators 9a and 9b.

The tissue model or phantom shown in Fig. 3 was designed to simulate the optical properties of a moderately-perfused finger. The tissue phantom consisted of two interweaved networks of randomly distributed plastic tubes (0.25 mm ID) embedded in a

liquid scattering medium. One network 10 was composed of rigid polystyrene tubing occupying about 2% of the total scattering volume; the other network 11, which occupied about 1% of the scattering volume, was composed of soft silastic tubing. The rigid tubing 10 was filled with a fixed volume of whole blood which simulated the reservoir of non-pulsatile blood in the skin. To simulate a small pulsatile increase in the blood volume, whole blood was injected into the network of silastic tubing. In testing, the intensity recorded before injection represented the non-pulsatile component (I_{dc}) and the difference between the intensity recorded before and after injection represented the pulsatile component of the diffuse intensity (I_{ac}).

Blood samples having a known hematocrit were prepared by mixing packed human red cells and plasma obtained from the blood bank. Before mixing, the initial hematocrit of the packed cells was determined by measuring the cell volume fraction in centrifuged capillary-tube samples. The scattering liquid in which the tubing networks were embedded consisted of a mixture of 0.99-μm-diameter polystyrene spheres 12 (Polyscience, Inc.), water, and glycerol in a glass-walled sample chamber (5.9 mm thickness). In one example, 1.3 vol.% of spheres were used in a 1:1 mixture of glycerol and water to obtain a transport-corrected scattering coefficient equal to 1.73 $mm^{-1}$and 1.26 mm^{-1} at 800 and 1300 nm, respectively (values were calculated using Mie scattering theory; the calculated anisotropy parameter of the spheres in the mixture was 0.91 at 820 nm and 0.83 at 1300 nm). Glycerol, which has a lower absorption coefficient than water at 1300 nm (0.044 mm^{-1} vs. 0.14 mm^{-1}), was added to reduce the absorption

coefficient of the mixture at 1300 nm to about 0.092 mm^{-1}. At 820 nm, the absorption coefficient of the water/glycerol mixture was very small (<0.003 mm^{-1}); therefore, absorption at this wavelength was mainly determined by the volume of blood in the tubing network.

To obtain reemittance measurements from live human skin, the instrumentation shown in Fig. 2 was modified slightly. As shown in Fig. 4, the fiber bundles 2 were replaced by a single optic fiber 13 and the light from both laser diodes 1a and 1b was focused on an end of optic fiber 13. An identical optic fiber 14 was attached to the photodiode 6. To adjust the distance between the source and detector fibers (13 and 14), a calibrated position was used. Figure 4 shows a human finger 15 positioned between optical fibers 13 and 14.

Photoplethysmograms were recorded holding the tip of the optic fiber 13 against the top surface of the index finger 15. A photodiode 6 contacted the bottom surface of the finger 15 via optic fiber 14. In another embodiment, optical fiber 14 was eliminated and the lower surface of finger 15 rested on photodiode 6. The output signals from the lock-in amplifiers were band-pass filtered (0.5 - 10 Hz) to separate the ac and dc intensity signals, which were subsequently processed using a microcomputer-based data acquisition system (not shown).

The intensity of light transmitted through a 1.85 mm thick sample of fresh, fully oxygenated whole blood at 800 nm and 1300 nm is shown in Fig. 3a as a function of blood hematocrit.

Even in this optically thin sample, the effects of multiple scattering are evident from the transmission

curves; at hematocrit values greater than about 50%, the intensity no longer exhibits an exponential dependence on hematocrit. This behavior is a consequence of the non-linear relationship between the concentration of scatterers (red cells) and the scattering coefficient, which is described by the scattering function f(H) in Eq. (2). Note from Fig. 3b, however, that the ratio between the optical densities measured at 800 nm and 1300 nm has a linear dependence on hematocrit over nearly the entire measurement range. As expected, the oxygenation state of the blood was found to have no discernible effect on light attenuation at either wavelength, confirming that these wavelengths are isobestic for Hb and HbO_2. These data demonstrate that, for a fixed sample thickness and optical configuration, the hematocrit of whole blood can be determined simply and rapidly by measuring the ratio of optical densities of samples at these two isobestic wavelengths.

Unlike in whole blood, the photon path lengths in skin tissue at 800 nm and 1300 nm are not well-defined; they depend on the concentration of the absorbing substances (mainly water and hemoglobin) and scatterers in the skin, as well as the dimensions of the illuminated volume. In Table 1 below, representative values of the optical parameters of blood and human skin, treated as a homogeneous medium, are given for λ = 800 nm and λ = 1300 nm. The blood absorption values were calculated according to Eqs. (3) and (4), using the measured absorption data plotted in Fig. 1; the scattering coefficient of blood was calculated by Mie theory (Bonner, Vol. 4, supra). The scattering coefficients shown in Table 1 were estimated using the surface-reemittance measurement technique discussed

above. According to the Table 1 values, the optical coefficients of the in vitro model used in the present experiments corresponded to those of a 10 mm-thick finger containing 1-3 vol.% of blood and 65 vol.% of water.

TABLE 1

Estimated Optical Parameters of Blood and Skin Tissues

	800 nm	1300 nm
Blood:		
μ_a (mm^{-1})	1.04 H	0.078H + 0.14
μ_s^* (mm^{-1})	11.5 f(H)	9.8 f(H)
Tissue:		
μ_a (mm^{-1})	1.04 HV_b	$(0.14+0.078H)V_b+0.14V_w$
μ_s^* (mm^{-1})	1.0	0.75

[a]Values are defined in terms of blood hematocrit (H), blood volume fraction (V_b), and water volume fraction (V_w). The function f(H) is defined in the text above.

Fig. 6 shows the results of two experiments in which the ratio $R = (1_{ac}/1_{dc})^{830}/(1_{ac}/1_{dc})^{1300}$ was measured as a function of hematocrit (H) using the in vitro tissue model. The ratio varied by a factor of about 2.5 over the range of hematocrits between 15% and 60%. The volume of blood in the rigid tubing network (denoted as "V_b" in the figure), which mainly affected the background absorption at 830 nm, did not appear to have a strong effect on the R vs. H relationship. The

theoretical curves shown in the figure, which were obtained using the photon-diffusion theory discussed above fit the experimental data well. To generate the theoretical curves, the ac-dc intensity ratio at each wavelength was calculated using Eq. (14), with l_t given by Eq. (12). The total absorption coefficient of the experimental scattering medium was calculated by adding the absorption coefficients of the water/glycerol mixture and blood (Table 1), according to Eq. (13), and the total scattering coefficient was assumed to be equal to that of the polystyrene spheres in the water/glycerol mixture.

As can be appreciated, the present invention provides a method and apparatus which can be used to non-invasively measure blood hematocrit by dual-wavelength, near-infrared photoplethysmography.

Although the present invention has been described with reference to particular means, materials and embodiments, from the foregoing description, one skilled in the art can ascertain the essential characteristics of the present invention and various changes and modifications may be made to adapt the various uses and characteristics thereof without departing from the spirit and scope of the present invention as described in the claims which follow.

WHAT IS CLAIMED IS

1. A method of measuring blood hematocrit which comprises:

directing first and second wavelengths of light through a blood sample;

determining the ratio between pulsatile and non-pulsatile diffuse transmittances measured at each of said first and second wavelengths of light from said blood sample; and

determining blood hematocrit of said blood sample from said ratio between pulsatile and non-pulsatile diffuse transmittances measured at each of said first and second wavelengths of light from said blood sample.

2. A method of measuring blood hematocrit according to claim 1, wherein said first and second wavelengths of light are near-infrared wavelengths.

3. A method of measuring blood hematocrit according to claim 2, wherein one of said first and second wavelengths of light is within the isobestic region of oxyhemoglobin and the other is within the isobestic region of deoxyhemoglobin.

4. A method of measuring blood hematocrit according to claim 3, wherein one of said first and second wavelengths of light is about 800 - 830 nm and the other is about 1300 nm.

5. A method of measuring blood hematocrit according to claim 1, wherein said blood sample comprises an in vitro blood sample.

6. A method of measuring blood hematocrit according to claim 1, wherein said blood sample comprises an in vivo blood sample.

7. A method of measuring blood hematocrit according to claim 6, wherein said blood sample is contained in a body part and said directed first and second wavelengths of light are directed to said blood sample from a location exterior to said body part.

8. A method of measuring blood hematocrit according to claim 1 further comprising simultaneously determining oxygen saturation utilizing a pulse oximetry technique.

9. An apparatus for measuring blood hematocrit which comprises:

a sample holder for receiving a blood sample;

a first light generating means for generating light within the isobestic region of oxyhemoglobin:

a second light generating means for generating light within the isobestic region of deoxyhemoglobin;

means for directing light from said first and second light generating means to said sample holder;

means for receiving light from said sample holder;

means for measuring pulsatile and non-pulsatile diffuse transmittances from said sample holder; and

means for determining a ratio of said measured pulsatile and non-pulsatile diffuse transmittances from said sample holder.

10. An apparatus for measuring blood hematocrit according to claim 9, wherein said means for directing light comprises an optical fiber.

11. An apparatus for measuring blood hematocrit according to claim 10, wherein said optical fiber comprises a bifurcated optical fiber.

12. An apparatus for measuring blood hematocrit according to claim 9, wherein said means to receive light from said sample holder comprises a photodiode.

13. An apparatus for measuring blood hematocrit according to claim 12, wherein said photodiode comprises a InGaAs photodiode.

14. An apparatus for measuring blood hematocrit according to claim 9, wherein said first and second light generating means comprise laser diodes.

15. An apparatus for measuring blood hematocrit according to claim 10, wherein said sample holder comprises means to receive a human body part which is held in close proximity with said optical fiber which directs light to the sample holder.

16. An apparatus for measuring blood hematocrit according to claim 9, further including first and second reference oscillators which synchronize the operation of said first and second light generating means and first and second lock-in amplifiers which receive signals from said means for receiving light from said sample holder.

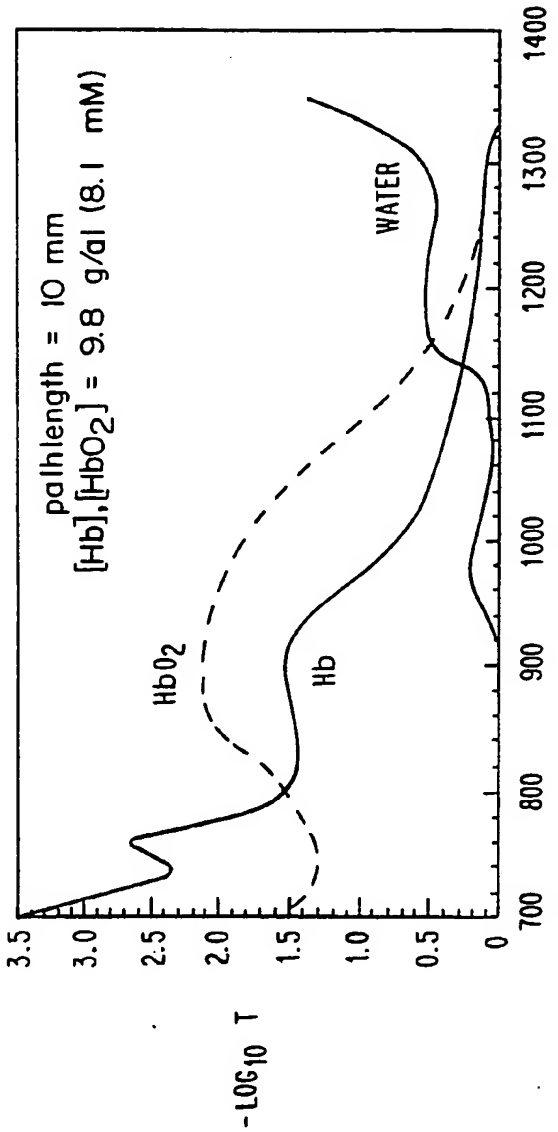
17. A tissue phantom for simulating optical properties of a perfused finger which comprises two interwoven networks of randomly distributed tubes, wherein one of said tube networks is filled with a fixed volume of a blood standard and another of said tube networks is adapted to be injected with a blood standard to simulate a pulsatile increase in blood volume.

18. A tissue phantom for simulating optical properties of a perfused finger according to claim 17, wherein said two interwoven networks of randomly distributed tubes are disposed in a solution which contains light scattering particles.

19. A tissue phantom for simulating optical properties of a perfused finger according to claim 18, wherein said solution comprises water and glycerol.

20. A tissue phantom for simulating optical properties of a perfused finger according to claim 17, wherein said tube network fill with said blood standard comprises rigid tubes and said another tube network comprises non-rigid tubes.

Figure 1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HbO2
Hb
WATER
-LOG10 T
WAVELENGTH (nm)
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2.5
2.0
1.5
1.0
0.5
0
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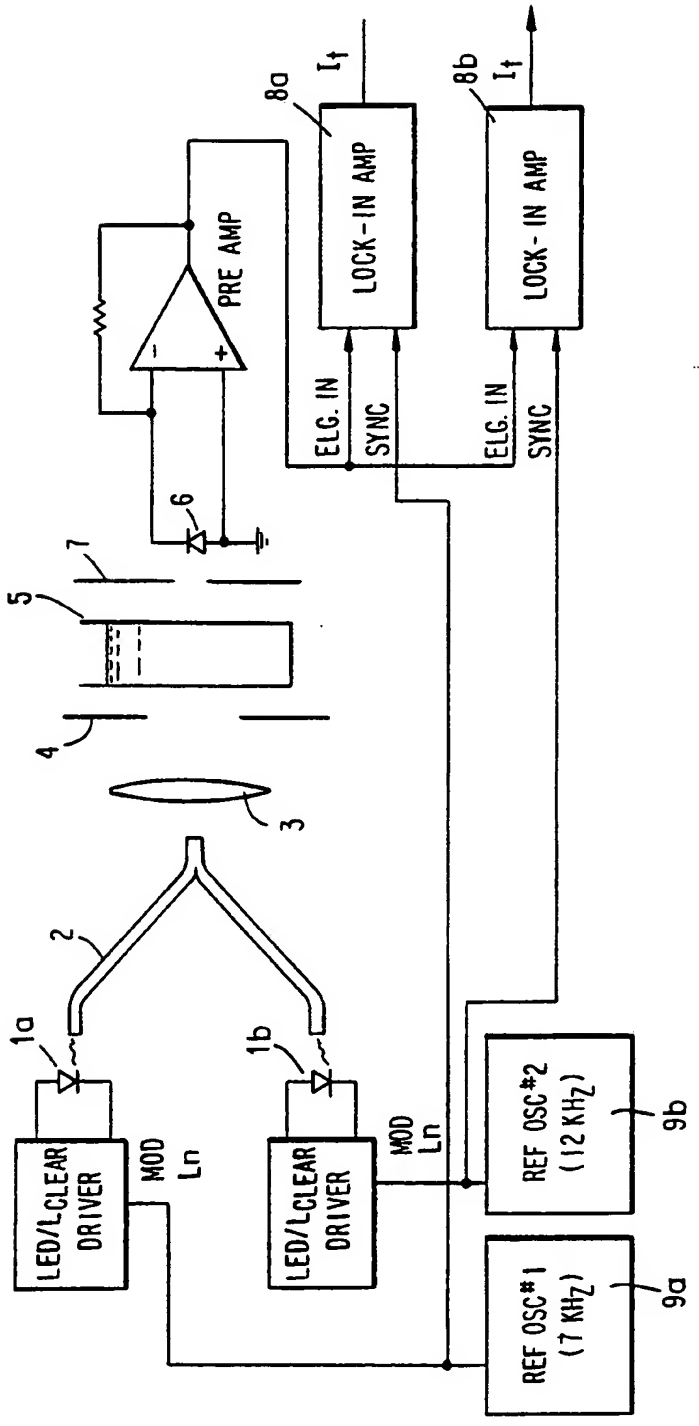
800
900
1000
1100
1200
1300
1400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8b
I_f
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LOCK-IN AMP
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SYNC
ELG. IN
SYNC
6
7
5
4
3
2
1a
1b
LED/L_{CLEAR} DRIVER
MOD Ln
LED/L_{CLEAR} DRIVER
MOD Ln
REF OSC#2 (12 KHz)
9b
REF OSC#1 (7 KHz)
9a

Figure 2

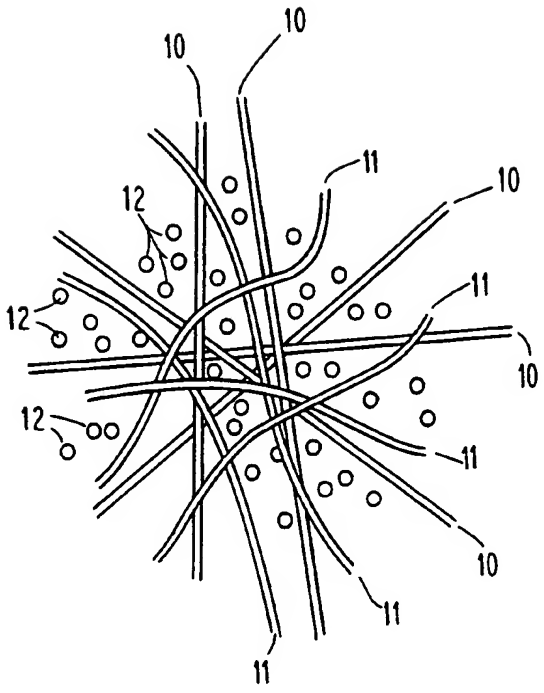
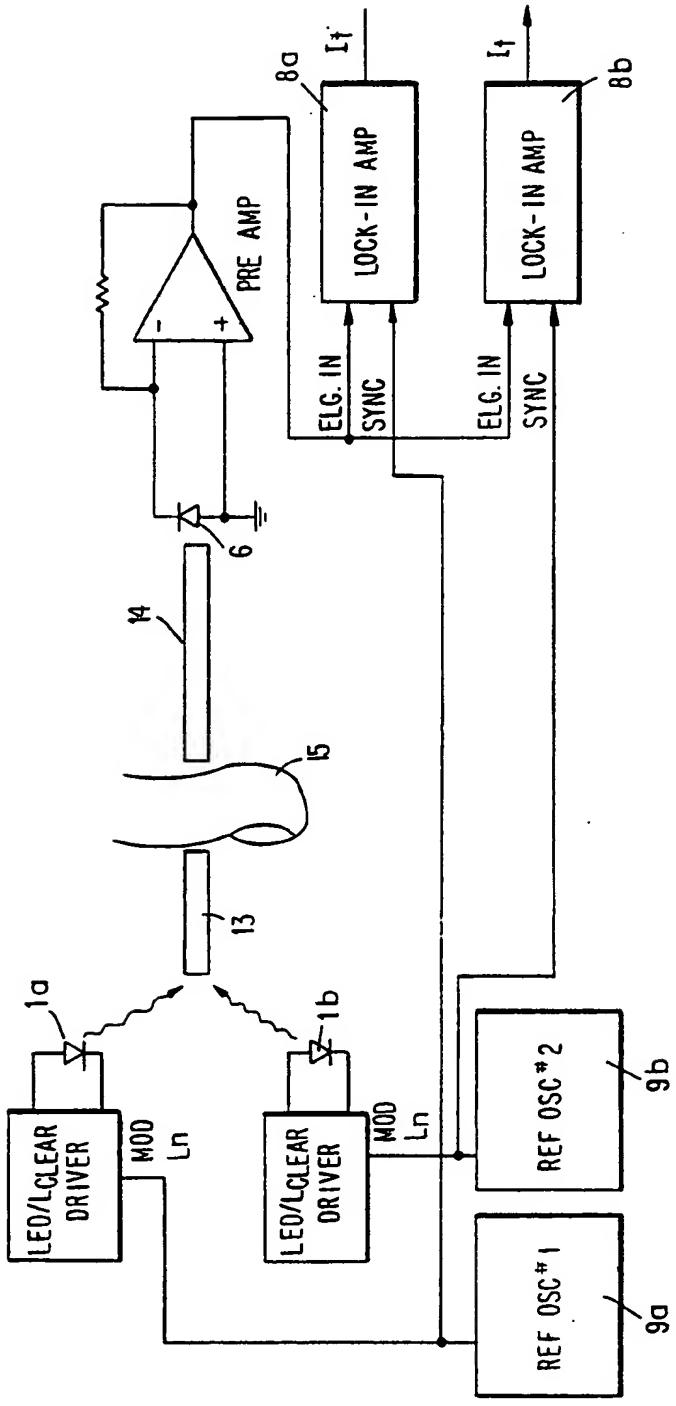


Figure 3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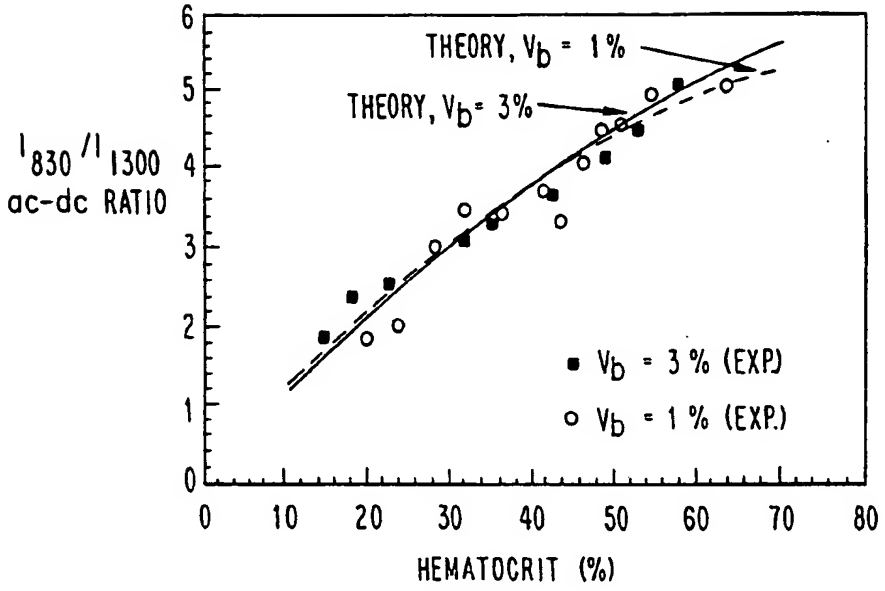
8b
LOCK-IN AMP
LOCK-IN AMP
ELG. IN
SYNC
ELG. IN
SYNC
PRE AMP
6
14
15
13
1a
1b
LED/LCLEAR DRIVER
LED/LCLEAR DRIVER
MOD
Ln
MOD
Ln
REF OSC*2
REF OSC*1
9b
9a

Figure 4

Figure 5a



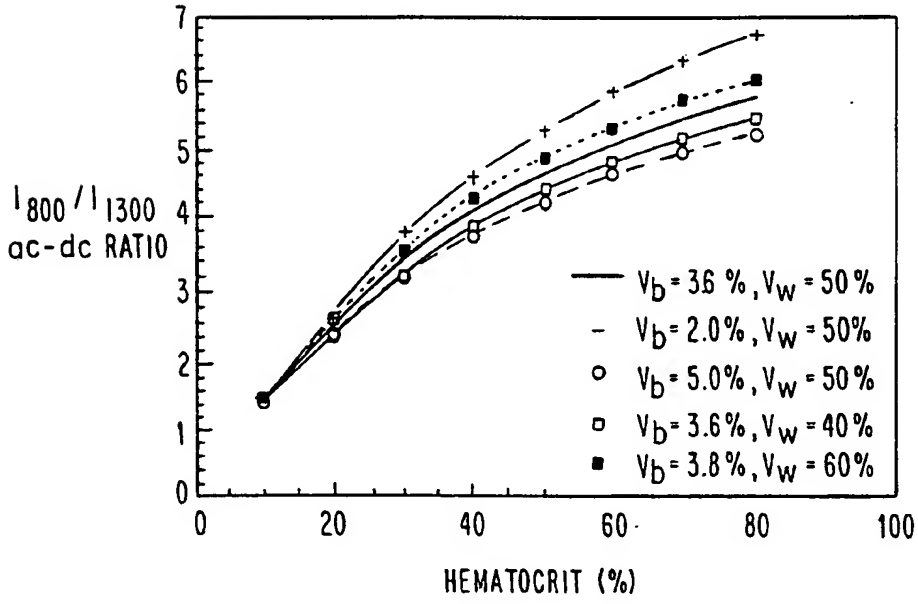
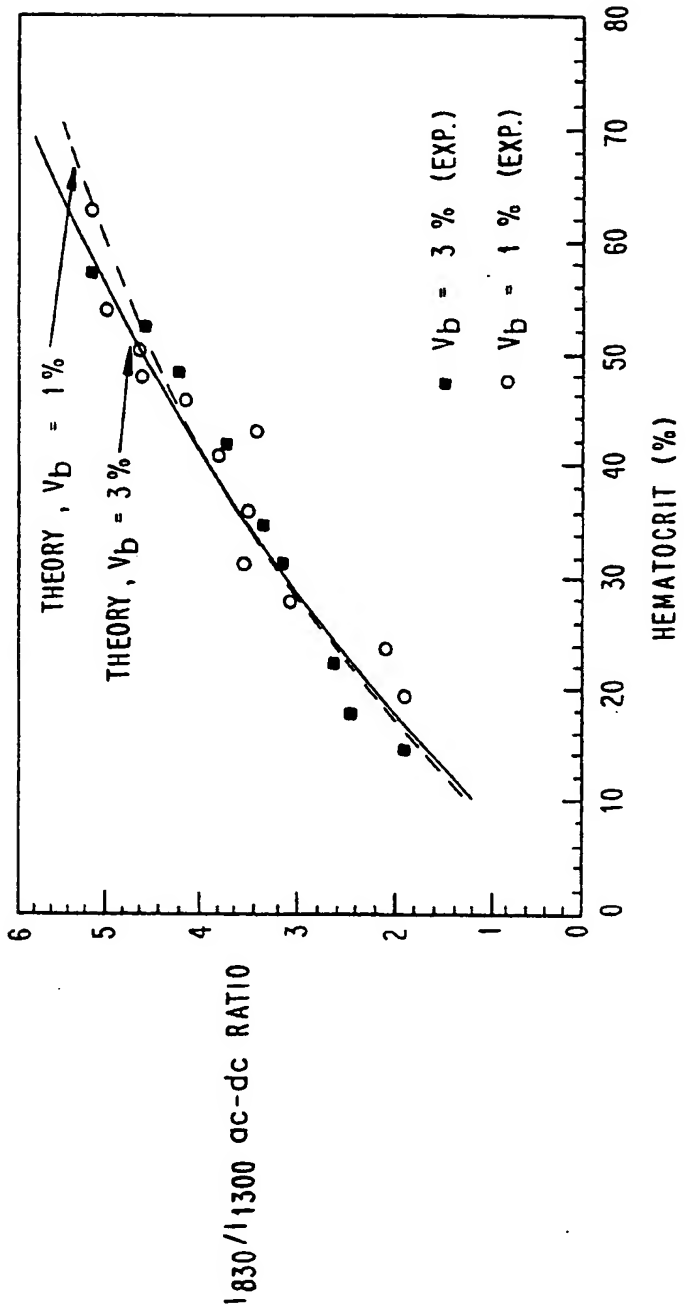


Figure 5b

Figure 6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THEORY , Vb = 3%
Vb = 3 % (EXP.)
Vb = 1 % (EXP.)
I830/I1300 ac-dc RATIO
HEMATOCRIT (%)
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1
2
3
4
5
6
0
10
20
30
40
50
60
70
80